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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,726	11/28/2000	Gyula Hadlaczky	24601-402E	7776

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EXAMINER	
HELMER, GEORGIA L	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/724,726	HADLACZKY ET AL.
	Examiner	Art Unit
	Georgia L. Helmer	1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-52 and 73-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-52 and 73-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6 January 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 January 2005 has been entered.

2. The Office acknowledges receipt of the 37 CFR 1.132 Declaration of Steven Fabijanski dated 7 December 2004. This 37 CFR 1.132 Declaration of Steven Fabijanski is the third 1.132 declaration of Fabijanski in this case, the first dated 16 July 2003 and the second dated 19 January 2004. Hereafter this third declaration is referred to as "Fabijanski Declaration 3".

Status of the Claims

3. New claims 73-113 have been added. Claims 50-52 and 73-113 are pending and are examined in this Office Action.

4. All rejections not addressed below have been withdrawn.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

6. An initialed and dated copy of Applicant's IDS form 1449 (6 January 2005) is attached to the instant Office action.

Claim Rejections - 35 USC § 112-second

7. Claims 50-52 and 73-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record. This rejection is repeated for reasons of record as set forth on pages 2 and 3 of the Office Action mailed 22 October 2003. Applicant's arguments filed 5 January 2005 have been fully considered but are not deemed persuasive.

At claim 92, line 2, the term "satellite artificial chromosome" is unclear. What is a satellite artificial chromosome? All claims reciting this term or its abbreviation ("SATAC") are included in the rejection.

Applicant recites various qualities of an satellite artificial chromosome:

- it contains "satellite DNA" (specification, p. 5). What is "satellite DNA" and how does it differ from other DNA?
- it is a "fully functional stable chromosome" (specification, p. 5).
- it provides an extra genomic locus for targeted integration of DNA (specification, p. 5).
- it is primarily made up of "repeating units of short satellite DNA" and are "nearly fully heterochromatic" (specification, p. 7).

Applicant traverses saying (Response of 6 January 2005, p.7 and 10) a SATAC is a chromosome that contains more heterochromatin than euchromatin, citing specification p. 7, 19 and 94–(Response of 6 January 2005, p. 9) that SATAC refers to a chromosome than contains satellite DNA and that contains more heterochromatin than euchromatin. Specifically, Applicant cites the specification p. 7 lines 15-20 which says that SATAC are primarily made up of repeating units of short satellite DNA and are nearly heterochromatic, so that without inserting heterologous DNA they contain no genetic information or contain only nonprotein encoding sequences such as rDNA; p. 10, lines 4-6, which sets forth that a SATAC is substantially all heterochromatin; and p. 94, lines 3-21. This says that the (mouse) megachromosome is composed primarily of heterochromatin as demonstrated by C-banding of the megachromosome which gives positive staining of constitutive heterochromatin, which shows that other than the terminal regions and the foreign DNA, the whole megachromosome appears to be heterochromatin. Assuming that mouse major satellite DNA is the main component of the pericentric constitutive heterochromatin of mouse chromosome and represents 10% of the total DNA, and using hybridization data, and "by comparing these segments with the pericentric regions of normal mouse chromosomes, that carry 15 Mb of major satellite DNA, the size of the blocks of major satellite DNA on the megachromosome was estimated to be ca. 30 Mb." Applicant's traversal is unpersuasive. The mouse megachromosome work is based on a number of assumptions, and relevance of this system to plants and plant SATACs is not apparent, since Applicant has not described plant megachromosomes.

The issue of how an artificial chromosome differs from a SATAC remains. If the ratio of chromatin is such that heterochromatin > euchromatin, and the quantity of heterochromatin is more than the quantity of euchromatin, how much is "more" ? Is it 50%, 10%, 1% or will one nucleotide suffice? In the absence of such a clear distinction, the term "SATAC" remains undefined by the specification.

The recitation of properties of a satellite artificial chromosome does not teach what the essential elements of satellite artificial chromosome are, nor does this make the metes and bounds of satellite artificial chromosome apparent.

Applicant traverses saying primarily (Response, p. 8) that since the term SATAC is recited in an issued claim (US 6,077,697), this term is presumptively definite (response, p. 8). Applicant's traversal is unpersuasive. First, the instant claims are effectively drawn to plant-functional SATACs, which are not claimed in the patents, except for claim 27 of 6,077,697. This Office Action and all subsequent actions which maintain this rejection will be reviewed and signed by the Group Director of Technology Center 1600.

Claim Rejections - 35 USC § 112 Written Description

8. Claims 50-52 and 73-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record, set forth on pages 4-5 of the Office Action of 22 October 2003. Applicant's arguments filed 6 January 2005 have been fully considered but are not deemed persuasive.

Applicant traverses asserting the specification provides detailed definitions and structural characterizations of a SATAC and each of its elements, so that it is clear that

Applicant was in possession of a SATAC as of the filing date of the instant application and as of its earliest priority date. Applicant further says the specification describes how plant artificial chromosome differs from other artificial chromosomes (Response, p. 12): "a mammalian artificial chromosome (MAC) is a piece of DNA that can stably replicate and segregate alongside endogenous chromosomes. It has the capacity to accommodate and express heterologous genes inserted therein. It is referred to as a mammalian artificial chromosome because it includes an active mammalian centromere. Plant artificial chromosomes...refer to chromosomes that include plant...centromeres" (specification, p. 16).

Applicant's traversal is unpersuasive. Applicant defines the artificial chromosome as being a piece of DNA having certain qualities. However Applicant's definition and description is given in terms of "chromosomes". Chromosomes consist of nucleic acids and proteins, the proteins being histone proteins as well as non-histone proteins, not naked DNA. It would appear that Applicant's description of artificial chromosome, as DNA, is lacking at least one family of components—the proteins. Furthermore, describing an artificial chromosome as DNA that can stably replicate and segregate alongside endogenous chromosomes, and having the capacity to accommodate and express heterologous genes inserted therein, fails to distinguish artificial chromosomes from "wild-type" chromosomes. "Wild-type" chromosomes can stably replicate and segregate alongside endogenous chromosomes, and have the capacity to accommodate and express heterologous genes inserted therein, as is known from the

literature, which abounds with examples of transgenic animals, fungi and plants, and many progeny generations of these transgenics.

Applicant traverses primarily that the instant Application provides exemplary SATACs evidencing Applicant's possession of the claimed subject matter (Response of 6 January 2005, p.14). Applicant says that the specification describes the generation of animal cell lines such as G3D5 and HID3 containing megachromosomes (exemplary SATACs), and that these cells lines have been deposited in the ECACC and gives accession numbers. Applicant's argument is unpersuasive. Overcoming a written description rejection under 112.1 cannot be overcome by deposit of biological material unrelated to the instant claims. The instant claims are drawn to plant-functional SATACs, which differ from the deposited animal SATACs in at least the presence of a plant centromere, as admitted by Applicant on p. 16 of the specification.

Applicant further asserts that the specification depicts the structures of SATACs schematically in Figures 2 and 3 of the specification (Response, p. 15). Applicant's assertation is unpersuasive. Figures 2 and 3 show schematic of complex macromolecular pathway starting with mouse chromosome #7 being transfected with foreign DNA, which DNA is described as specific λ DNA. The other components are macromolecular complexes, comprising for example heterochromatin and euchromatin.

Applicant, noting that the instant Application is a CIP of US 6,077,697, which contains issued claims directed to methods of producing and isolating SATAC as well as composition claims directed to isolated SATACs, asserts that therefore these provide SATACs and their structural elements. Applicant asserts the issued patents

and the instant case are related as CIP's of a common parent and thus Applicant has demonstrated possession of SATACs as of the earliest filing date (Response of 6 January 2005, p. 20). Applicant's traversal is unpersuasive. First, only one of the patented claims is drawn to plant-functional SATACs, as instantly claimed. Second, this Office Action has been reviewed by a PTO Director as stated above.

Applicant fails to provide Written Description with respect to the structural and physical characteristics of the claimed invention. There is no structural description, other than saying that a SATAC is a piece of DNA, of what comprises a SATAC, particularly a plant-functional SATAC. Applicant fails to mention or describe in any way, other required components, namely the proteins. Therefore Applicant is claiming a genus of macromolecular components, yet there is no description to the structural features that define the genus, as required by Lilly, cited previously.

Applicant traverses primarily (Response, p. 27) that numerous publications exist which describe protein components of chromosomes, that "a satellite artificial chromosome is chromosome with particular features", that the application discusses protein components of chromosomes and how one skilled in the art can distinguish a satellite artificial chromosome from an endogenous chromosome using such features. Applicant's traversal is unpersuasive. Applicant has provided no evidence of appropriate protein association with any plant satellite artificial chromosome nor any evidence of appropriate recruitment of specific histone or non-histone proteins by any plant satellite artificial chromosome.

Claim Rejections - 35 USC § 112.1 Enablement

9. Claims 50-52 and 73-113 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record. This rejection is repeated in part for reasons of record as set forth in the Office Action mailed 22 October 2003 on pages 6-8. Furthermore, the Examiner now relies upon Ohgawara et. al. (1983) and Potrykus (1990) to demonstrate the unpredictability inherent in liposome-mediated plant transformation (claims 52, 75,82, 102 and 109); and in plant transformation and maintenance of the exogenous DNA in plants as generally claimed, particularly in monocots (claims 88-91, 94 and 98-99).

Ohgawara, et. al., (1983) studying liposome-encapsulating plasmid DNA by plant protoplasts and the molecular fate of foreign DNA, found variations in DNA uptake among protoplasts from different plant species (p. 145 Abstract). In fact, after one week in culture, in only one plant, D. carota (carrot) was even a trace amount of plasmid DNA detected (p. 147, column 2, top ¶).

Potrykus (1990), reviewing gene transfer to cereal plants (monocots), teaches the general recalcitrance of monocots to transformation; and discusses the variability relating to gene transfer, considers the biology of gene transfer, saying that a transgenic plant can only result from integrative transformation in a totipotent cell or a cell that has a clonal connection to the "germline". Issues of concern here are (1) Not all plant cells are totipotent. (2) Plant cells differ in their capacity to respond to triggers, a phenomenon termed *competence*. (3) Cells from which it is hoped to regenerate transgenic plants must be competent for both regeneration (in a broad sense) and integrative transformation. (4) Plant tissues are composed of cells competent for many

different responses. Considering the two states of competence essential for recovery of transgenic plants the following situation has to be considered: a/ A very small minority of cells in plant tissues will be competent for both transformation and regeneration. b/ Others will be competent for transformation or regeneration. c/ A large fraction of the cell population will be potentially competent, meaning that given the correct treatment they will have the potential to shift to the competent state. d/ A variable proportion of cells will not even be potentially competent, but will be non-competent. (5) The relative composition of cell population in tissues is determined by the genotype, the type of organ, the developmental state of the organ, and even the individual history of the experimental plant (p. 538, column 1, bottom ¶).

Of 23 different plant transformation techniques, only two, direct gene transfer into protoplasts and microprojectile bombardment, have shown any promise in either producing transformed monocot cells, whole transformed monocot plants, or transformed offspring (see pages 536-537). As the claims broadly read on any transformed plant of any of a multitude of unrelated species; and since particularly claims 88-91, 94 and 98-99 read on a multitude of recalcitrant monocotyledonous species; the specification does not provide any teachings of plant transformation of any species, which would be required to overcome the evidence of unpredictability inherent in obtaining transformed plant cells as claimed.

Microinjection (as claimed in claims 52, 76, 83, 103 and 110) uses microscopic devices to deliver DNA to defined cells in such a way that the infected cell survives and proliferates. Transfer to structures of more than one cell can only produce transgenic

chimeras, and transgenic offspring can only be expected if the transgenic sector contributes to the floral meristems, so that no transgenic offspring have been produced (p. 541, column 1, middle ¶).

Applicant's arguments filed 6 January 2005 have been fully considered but are not deemed persuasive. Applicant largely refers to the Fabijanski declaration of 7 December 2004.

The declaration of Fabijanski dated 7 December 2004 (Fabijanski Declaration 3) has been carefully considered and is unpersuasive.

Fabijanski Declaration 3 describes generation of whole plants containing a SATAC (Declaration p. 3) by the following steps:

(1) construction of heterologous DNAs—

(a) Vector pAgIIa, a vector containing a region of homology to tobacco pericentric DNA,(the central AT-rich region of a tobacco rDNA intergenic spacer capable of amplification) as well as a detection marker containing mouse satellite DNA , and

(b) a second DNA, the "targeting DNA" containing a region of homology to pericentric DNA sequences (a 1.7 Kb portion of the 26S rDNA coding region);

(2) introduction of the DNAs into plant cells and selection—

(c) by introduction of Vector pAgIIa DNA and "targeting DNA" into tobacco protoplasts using transfection, followed by culture of plant tissue microcalli under selective antibiotic conditions.

(3) Identification of amplified DNA molecules;

(4) Regeneration of transgenic plants containing SATACs

(5) Generation of transgenic plants containing SATAC by cell fusion using interspecific fusion of SATAC-containing N. tabacum protoplasts with protoplasts of N. glauca (Declaration 3. p. 5-7).

The Declaration of Fabijanski (Fabijanski Declaration 3) provides information of the production of a plant SATAC, and the production of transgenic tobacco plants containing the plant SATAC. However the method of Fabijanski, as set forth in Fabijanski Declaration 3, is not supported by the specification as of the date of filing.

Fabijanski employs information and biological materials not available as of the earliest date of filing, namely April 1996. Fabijanski employs DNA sequences (Genebank X76056) not available until 27 September 1996 at the earliest. See Genebank accession number Y08422 (Applicant's IDS of 6 January 2005). Borisjuk et. al. (Plant Mol Biol 35, 655-660, 1997), also cited by Applicant's IDS of 6 January 2005, provides information relating to the tobacco rDNA intergenic spacer regions capable of amplification, which Fabijanski used. Borisjek et. al. provided the information relating to the homology to tobacco pericentric sequences.

Furthermore, the Fabijanski method employs in step 1 (Construction of heterologous DNAs) two different constructs: *Vector pAglla* containing a "sequence with homology to the pericentric DNA" and selectable markers, and a *targeting DNA* construct containing sequences with homology to the pericentric DNA sequences. Fabijanski uses two different defined sequences having specified properties for this purpose, as discussed above. One of the DNA sequence used is small (334 bp) and the other is larger (1.7 kb), suggesting that sequence size may be an important

consideration. Are these sequences with "homology to the pericentric DNA" interchangeable? The DNA sequences used have specific characteristics, such as homology to pericentric DNA, which recommended their use in the method of Fabijanski. Why are these sequences used preferentially in this example?
The specification describes (p. 42-48) in vitro construction of artificial chromosomes, whereby the artificial chromosome can be constructed by assembling the structural and functional elements that contribute to a complete chromosome capable of stable replication and segregation alongside endogenous chromosomes, and physically ligating the appropriate components. These elements include identification and isolation of components of the artificial chromosome starting with animal cell lines on deposit (p. 43). The elements enumerated are centromeres (p. 44-45), telomeres, megatreplications, filler heterochromatin and selectable markers (p. 46-47). Surely this is not the method of Fabijanski as set forth in the Fabijanski Declaration 3.

See Genentech, Inc. v. Novo Nordisk, A/S, 42 USPQ2nd 1001, 1005 (Fed. Cir. 1997).

See In re Glass, 181 USPQ 31, 34 (CCPA 1974), which teaches that references published after the filing date of an application may not be relied upon for the enablement of the specification. Furthermore, the mere germ of an idea does not constitute an enabling disclosure, and the specification, not the knowledge of one skilled in the art must supply the enabling aspects of the invention.

The specification as filed gives no information or guidance the obtaining a plant origin of replication or a plant centromere(s), or plant telomere(s) which would function

as desired to produce a transgenic plant transgenic for an artificial chromosome. Undue experimentation would be required to determine what DNA sequence(s) would function as desired in the claimed invention. What DNA sequence containing homology to what DNA would be appropriate as pericentric DNA? Applicant must provide sufficient guidance to address these issues and those above. Without such guidance the experimentation required would not be routine, but would be undue. This would impose a burden on the skilled artisan, without a reasonable expectation of success.

Applicant is not enabled for the claimed invention as commensurate in scope with the claims.

Applicant traverses saying primarily (Response, p. 19) that the working examples are exemplified in mammalian cells and the Applicant explains that these methods are applicable to any plant and animal cell type and any plant or animal species of SATAC. Applicant's traversal is unpersuasive, as discussed previously. Applicant's assertions, that plant and animal SATACs and hosts transformed therewith are the same, are refuted by the evidence provided by the Examiner in the original enablement rejection found on p. 6-8 of the Office Action of 22 October 2003; the newly cited Ohgawara et. al. and Potrykus references demonstrating the unpredictability inherent in the introduction and maintenance of heterologous DNA into plant cells and whole plants; and the reliance of Fabijanski Declaration 3 on numerous plant DNA molecules and plant transformation techniques not disclosed by the specification or present in the deposited cell lines.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 50, 51, 52, 73, 80, 88-92, 94-96, 98-100, and 107 are anticipated by Richards et. al. (US 5,270,201, issued 14 December 1993).

The instant claims are drawn to a method for producing a transgenic plant comprising introducing a satellite artificial chromosome (SATAC) into a plant cell and growing the plant cell under conditions to produce a transgenic plant.

Since the term "satellite artificial chromosome" (SATAC) is indefinite, this term is interpreted broadly to encompass "artificial chromosomes".

Richards et. al. teach a method of making an artificial plant chromosome (column 33, Example 19 and Figure 10(C)), using it to transform plant cells (column 7, lines 3-6), regenerating a whole plant (column 10, lines 34-37), wherein the plant cell is a protoplast (column 10, lines 35-36), wherein the artificial chromosome encodes a gene product (column 10, lines 53-56), wherein the artificial chromosome is introduced by direct DNA transfer (column 7, lines 3-6), and wherein the plant cell is from a monocot, a dicot or an algae (column 10, 34-38).

The prior art herbicide resistant form of a normally occurring enzyme is a heterologous encoded gene product.

Accordingly, Richards et. al. anticipate the claimed invention.

Remarks

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0796. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Transgenic Plants –art unit 1638
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